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Diarrheal Diseases

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Diarrhea is a complex of symptoms and signs, usually defined as an increased number of stools of liquid or semiliquid consistency passed during a twenty-four-hour period. Although a considerable variety of definitions can be found in the literature (Snyder and Merson 1982), recent studies have tended to consider more than three stools passed in twenty-four hours of observation as an indication of diarrhea after the age of three months (WHO 1988c). The word "diarrhea" is also used in programmatic and public health contexts, although not typically in clinical contexts, to embrace dysentery. Dysentery is usually characterized by the presence of blood in the stools, with or without excessive looseness or frequency.

Considerable differences of opinion still exist as to the minimum number of healthy days that marks the end of a diarrheal episode, ranging from forty-eight hours (WHO 1988c) to two weeks (Scrimshaw and others 1961). Episodes tend to be self-limiting, generally lasting for less than seven days. Studies in several developing countries have shown that 3 to 20 percent of acute diarrheal episodes in children under five may become persistent, lasting for at least fourteen days (WHO 1988b).

A variety of enteric pathogens—including bacteria such as enterotoxigenic *Escherichia coli*, enteropathogenic *E. coli*, *Salmonella*, *Shigella*, *Vibrio cholerae*, and *Campylobacter jejuni*; viruses such as rotavirus; and protozoa such as *Giardia lamblia*, *Entamoeba hystolytica*, and *Cryptosporidium*—can cause diarrhea (Farthing and Keusch 1989). The specific pathogens of greatest importance to public health vary according to age of the patient and the geographical setting. For example, rotavirus is a significant cause of severe diarrhea in children under two years of age in developing countries, and *Salmonella* and *Campylobacter* are primary causes among adults in industrialized countries who consume poultry raised in factory-farming conditions.

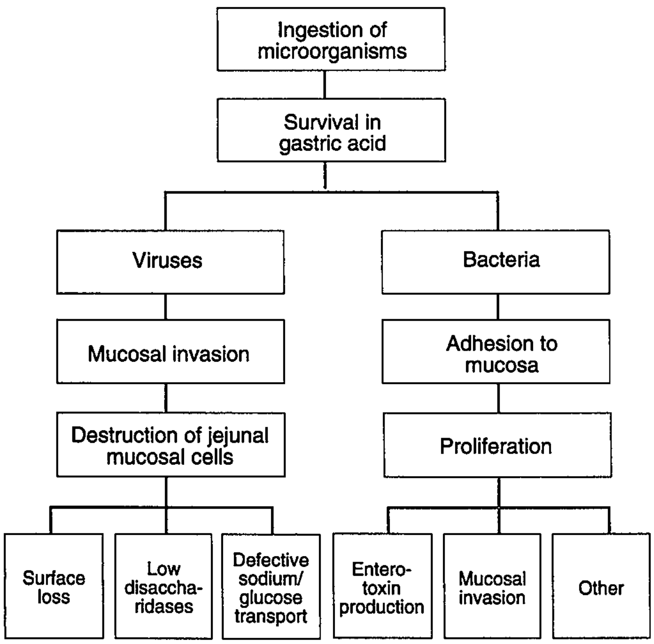
Other causes of diarrhea, considered to be relatively unimportant in developing countries, include food intolerance, especially lactase deficiency and allergies to animal protein, granulomatous diseases of the gut, and tumors elaborating gastrointestinal hormones (Rohde 1986). Diarrhea may also be associated with infections outside the intestinal tract, such as malaria, measles, and respiratory infections and is a prominent feature in acquired immunodeficiency syndrome (AIDS).

The pathogenesis of infectious diarrhea has been extensively studied, and the primary pathogenic mechanisms are summarized in figure 5-1. Some of these pathogenic processes, especially those relating to the production and action of the enterotoxins of *E. coli* and *V. cholerae*, are understood in great detail. This understanding has opened the way to the production of sophisticated vaccines, including the live, genetically engineered, vaccine strains.

The risk of diarrheal morbidity and mortality is greater among families of lower socioeconomic status and in conditions of poor personal and domestic hygiene. Low family income (Manderson 1981; Stanton and Clemens 1987b), lack of luxury items (Huttly and others 1987), living in a one-room house (Stanton and Clemens 1987b), living in a house with an earthen floor (Bertrand and Walmus 1983), lower maternal education (Bertrand and Walmus 1983), lower occupational status of the head of the family (Islam, Bhuiya, and Yunus 1984), and unclean living conditions (Bertrand and Walmus 1983; Huttly and others 1987; Taylor and others 1986) have all been associated with increased risk of diarrheal morbidity and mortality.

The risk of diarrheal morbidity and mortality is higher among infants who are not breastfed (Feachem and Koblinsky 1984). More recent studies in developing countries have confirmed the very substantial role of breastfeeding in protecting infants against diarrheal incidence, severity, and mortality (Briend, Wojtyniak, and Rowland 1988; Clemens and others 1986; Huttly and others 1987; Mahmood, Feachem, and Huttly 1989; Martines 1988; Victora and others 1987). Several studies indicate a risk of increased diarrheal duration and severity among the malnourished (Bairagi and others 1987; Black, Brown, and Becker 1984a; Black and others 1984; Chen, Huq, and Huffman 1981; Palmer and others 1976). Recent studies in Sudan and Mexico have suggested that malnutrition also increases the risk of frequent diarrheal episodes (Samani, Willet, and Ware 1988; Sepúlveda, Willet, and Muñoz 1988). Although information is scarce on the role of low birth weight as a determinant of diarrheal morbidity (Ash-

Figure 5-1. Primary Pathogenic Mechanisms for Infectious Diarrheal Diseases



Source: Candy and Phillips 1986.

worth and Feachem 1985b), the association between intrauterine growth retardation and impaired immunocompetence, and the strong association between low birth weight and diarrheal mortality in infancy in developing countries (Barros and others 1987), suggest that low birth weight is a risk factor for diarrheal severity and mortality.

Diarrhea can lead to dehydration and early death, particularly in young children (Gordon and others 1968; Snyder and Merson 1982), and to impaired growth and nutritional status among the survivors. The effect of diarrhea on infant and child growth and nutritional status is the outcome of a complex interplay of host, pathogen, and sociocultural factors, which may cause decreased food intake (Briscoe 1979; Brown and others 1985; Hoyle, Yunus, and Chen 1980; Khan and Ahmad 1986; Martorell and others 1980; Mata and others 1977; Nabarro and others 1988), malabsorption (Chen 1983; Molla, Molla, and Khatun 1986; Rosenberg, Solomons, and Schneider 1977; Scrimshaw 1977), loss of endogenous nutrients (Chen 1983; Sarker and others 1986), and increased metabolic rate (Beisel 1977; Chen 1983; Keusch and Katz 1979; Keusch and Scrimshaw 1986).

Longitudinal studies have detected a significant effect of diarrheal episodes on the growth of infants and children (Bairagi and others 1987; Black, Brown, and Becker 1984b; Cole and Parkin 1977; Condon-Paoloni and others 1977; Guerrant and others 1983; Martorell and others 1975; Martorell and others 1977; Nabarro and others 1988; Rowland, Rowland, and Cole 1988; Zumrawi, Dimond, and Waterlow 1987). The wide range of effects recorded have been variously attributed to the severity or duration of diarrheal episodes, the nutritional effectiveness of case management, and the extent of catch-up growth (Black, Brown, and Becker 1983; Brown and others 1985; Keusch and Scrimshaw 1986; Khan and Ahmad 1986; Miall, Desai, and Standard 1970; United Nations University 1979; Whitehead 1977).

Despite diarrheal incidence and severity being lower among adults, diarrhea may still represent a significant portion of total adult morbidity in developing countries. In Nigeria, diarrhea was associated with 20 percent of all illnesses in adults (Huttly and others 1987) and accounted for a median of 23 percent (range 5–41 percent) of disability days per year among adults age fifteen through forty-four in Pakistan, Indonesia, Nepal, and Ghana (Grosse 1980). In rural Bangladesh, diarrhea accounted for 14 percent of the total mortality among the population over forty-five years old surveyed between 1980 and 1983 (BRAC, 1987).

The Public Health Significance of Diarrhea

The current levels and trends of diarrhea morbidity and mortality in the developing world, and the probable patterns of morbidity and mortality in the next century are examined in this section.

Current Levels and Trends in the Developing World

Information on the current levels and trends in the incidence and mortality due to diarrhea is reviewed in the following paragraphs.

MORBIDITY. Measurements of diarrheal incidence depend on such factors as what definition of diarrhea is used, the frequency of surveillance, and the location of the study population (Snyder and Merson 1982). Since 1981, the Diarrhoeal Diseases Control Programme of the World Health Organization (WHO/CDD) has promoted a series of surveys to measure diarrheal morbidity and mortality rates using a consistent methodology (WHO 1987b, 1988c). Results from 276 surveys conducted in sixty countries between 1981 and 1986 are summarized in table 5-1. They indicate that, on average, children under five years of age in developing countries suffer 3.5 episodes of diarrhea per year. Excluding the Americas, where relatively few surveys have been undertaken, the highest rates were found in Sub-Saharan Africa and the lowest in Asia, especially in China and other countries in the Western Pacific region.

In order to estimate diarrheal morbidity rates among older age groups, for which information is scarcer, the estimates of relative incidence of diarrheal episodes in the older age groups adopted by the Committee on Issues and Priorities for New Vaccine Development of the Institute of Medicine of the United States (U.S. Institute of Medicine 1986) were applied to the WHO/CDD morbidity rates. Diarrheal incidence was estimated to be four to six times lower for those between five and fourteen years old, and thirteen to sixteen times lower for those

Table 5-1. Morbidity in 276 Surveys in Children Aged Four Years and Younger Using the WHO/CDD Methodology, 1981–86

Region	Surveys	Countries	Annual incidence (episodes/child/year)[a] Median	Range
Latin America and the Carribean	12	8	4.9	0.8–10.4
Sub-Saharan Africa	67	22	4.4	1.6–9.9
Middle East and North Africa	47	10	2.7	2.1–10.8
Asia and the Pacific	150	20	2.6	1.1–5.7
India	—	1	2.7	—
China	—	1	1.2	—
Other	—	1	2.6	—
All regions	276	60	3.5	0.8–10.8

— Not available.

Note: Surveys were conducted mainly in geographically limited areas. If more than one survey was conducted in any country, the median for the country was used to calculate the regional and global medians.

a. Survey estimate was adjusted for seasonality when appropriate data were available.

Source: Unpublished World Health Organization data.

beyond the age of fourteen years, than that observed among children under five (table 5-2).

Independent longitudinal studies largely confirm these estimates of diarrhea incidence in Latin America presented in table 5-2. In a poor periurban population in the north of Brazil, Giugliano and others (1986) recorded 4.8 episodes per year for children from birth to thirty-five months and 0.2 episodes per year for adults. Guerrant and others (1983), studying a poor urban group in northeast Brazil, found similar rates for young children but substantially higher ones for adults, for whom they estimated more than one episode per adult per year.

Diarrheal rates presented for Sub-Saharan Africa (table 5-2) are substantially lower than those estimated from cross-sectional surveys by Huttly and others (1987) in Nigeria (14 episodes per year among children six months through eleven months and 2.5 episodes per year among adults). Diarrheal rates described by Georges and others (1987) in the Central African Republic (7 episodes per child per year among children under five), although higher than the average of those presented for the region, were still within the range of the WHO/CDD survey findings from which the presented values were derived. A lower incidence (1.9 episodes per child per year)—but also within the range measured in the WHO/CDD surveys—was described among children under four years of age in rural Ghana (Biritwun and others 1986). Kirkwood (1991) provides a comprehensive review of knowledge of diarrhea epidemiology in Sub-Saharan Africa. Incidence rates presented for North Africa and the Middle East are similar to those described by el-Alamy and others (1986) among adults and children in rural Egypt.

Recently the epidemiology of persistent diarrhea (diarrhea lasting at least fourteen days) has been the focus of particular investigation. In rural northern India, Bhan and others (1989) report a low incidence of persistent diarrhea of 0.06 episodes per child per year in children under six years of age, with a peak incidence of 0.3 episodes per child per year in infants. Persistent episodes made up 10 percent of all episodes in children under six years and 22 percent of all episodes in infants under one year. In rural Bangladesh, Huttly and others (1989) report an incidence of persistent diarrhea of 0.6 episodes per child per year in children under five years of age (16 percent of all episodes). In the first half of infancy, persistent episodes comprised one-quarter of all episodes.

No evidence could be found in the literature of a fall in incidence rates of diarrhea during the past fifteen years. Snyder and Merson (1982), using active surveillance studies conducted between 1954 and 1979, estimated that diarrheal incidence in developing countries averaged 2.2 episodes per child per year. Comparing this value with the 3.5 episodes per child per year derived from cross-sectional survey data collected between 1981 and 1986, we must conclude that it is unlikely that any significant reduction in diarrheal incidence has occurred in the period between 1970 and 1985, particularly as cross-sectional surveys are likely to underestimate morbidity rates.

Table 5-2. Estimated Annual Diarrheal Morbidity Rates Region and Age, 1985

Region	Age (years) 0–4	5–14	15–59	>59
Latin America and the Carribean	4.9	1.2	0.3	0.3
Sub-Saharan Africa	4.4	0.9	0.3	0.3
Middle East and North Africa	2.7	0.5	0.2	0.2
Asia and the Pacific	2.6	0.4	0.2	0.2
All regions (median)	3.5	0.7	0.2	0.2

Note: Rates were calculated as episodes per person per year. Rates for children aged four years and younger were derived from CDD mobidity survey (table 5-1). Other rates were estimated according to relative incidence rates by age adopted by the Institute of Medicine 1986.

Source: Unpublished World Health Organization data. Rates were calculated by the authors.

MORTALITY. Available data on diarrheal mortality tend to be less reliable than those on morbidity. The only global data source available was generated during the WHO/CDD morbidity and mortality surveys (table 5-3). Some of the information on mortality was considered implausible by WHO, a situation that was attributed to lack of training or supervision of the surveyors (WHO 1988c). In addition, the survey method used, the interviewing of heads of households, who were asked to recall the deaths of family members in the past year, is regarded skeptically by some demographers and may greatly underestimate mortality rates (Timaeus and Graham 1989). The information in table 5-4, although the best presently available, should be regarded with caution. Estimates of diarrhea case-fatality rates by age that were made by the U.S. Institute of Medicine (1986) were used to calculate mortality rates of those beyond the age

Table 5-3. Mortality in 276 Surveys in Children Aged Four Years and Younger, Using WHO/CDD Methodology, 1981–86

Region	Surveys	Countries	Diarrhea Mortality Rate (deaths/1,000 children/year) Median	Range	Diarrhea deaths as percentage of total deaths (median)
Latin America and the Carribean	12	8	4.2	1.2–9.2	35
Sub-Saharan Africa	67	22	10.6	3.1–54.9	38
Middle East and North Africa	47	10	5.8	1.0–25.3	39
Asia and the Pacific	150	20	3.2	0.0–17.2	29
India	—	1	3.2	—	—
China	—	1	0.0	—	—
Other	—	18	3.3	—	—
All regions	276	60	6.5	0.0–54.9	36

— Not available.

Note: Surveys were conducted mainly in geographically limited areas. If more than one survey was conducted in any country, the median for the country was used to calculate the regional and global medians.

Source: Unpublished World Health Organization data.

of four years shown in the table. Case-fatality rates were estimated to fall from 2 per 1,000 among children under five, to 0.4 per 1,000 among those between five and fourteen years and 0.3 per 1,000 among persons between fifteen and fifty-nine years. A slight increase, to 0.5 per 1,000, was estimated for members of the population age sixty years and older.

Estimates of adult mortality due to diarrhea for developing countries with adequate vital registration systems are reported by Feachem and others (1992). Estimates of the risk of death from diarrhea between ages fifteen and fifty-nine vary from 0.01 percent (for example, in Argentina) to 3 percent in Guatemala. The proportion of deaths due to diarrhea was reported to be roughly 4 percent in India in persons aged fifteen through fifty-four years and 2 percent in Kenya in persons aged fifteen through sixty-four years (Feachem and others 1992).

Diarrheal mortality appears to have fallen substantially in many areas during the past fifteen years. Indications of this trend are reported from Egypt (el-Rafie and others 1990; Egypt, National Control of Diarrheal Diseases Project 1988), Thailand (Phonboon and others 1986), Brazil (Benicio and others 1987; Monteiro and Benicio 1989), Cuba (Riveron-Corteguera and Muñoz 1982) and Costa Rica (Mata 1981). The data from Egypt and Costa Rica indicate that this reduction in diarrheal mortality rates has been accompanied by reductions in general childhood mortality rates during the same period, in a way that suggests that diarrhea has not been replaced by other causes of death.

Diarrheal mortality in children under five was calculated by Snyder and Merson (1982) to be 13.6 deaths per 1,000 from data collected between 1956 and 1979, whereas a median value of 6.5 deaths per 1,000 was estimated by the WHO/CDD morbidity-mortality surveys (table 5-3). These latter data may, as explained above, be substantial underestimates. The case-fatality rates in children under five years old used by the U.S. Institute of Medicine (1986) increases the mortality rate to 7.1 per 1,000, still 48 percent lower than that calculated by Snyder and Merson (1982) for the period 1956–79. This fall in diarrheal mortality can be attributed reasonably to a fall in the case-fatality rate during the time. Current case-fatality rates vary widely: for children under five years they were found to be 0.8 per 1,000 in Bangui, Central African Republic (Georges and others 1987), 3 per 1,000 in rural Egypt (el-Alamy and others 1986), 3.6 per 1,000 in rural northern India (Kumar, Kumar, and Dutta 1987), and 5.4 per 1,000 in rural Indonesia (Nazir, Pardede, and Ismail 1985). Nevertheless, these values

Table 5-4. Estimated Annual Diarrhea Mortality Rates, by Region and Age, 1986

Region	Age (years) 0–4[a]	5–14	15–59	> 59
Latin America and the Carribean	4.2	0.5	0.1	0.1
Sub-Saharan Africa	10.6	0.4	0.1	0.1
Middle East and North Africa	5.8	0.2	0.1	0.1
Asia and the Pacific	3.2	0.2	0.1	0.1
All regions (median)	6.5	0.3	0.1	0.1

Note: Rates were calculated as deaths per 1,000 persons per year. Rates for children aged four and younger were derived from CDD mortality surveys (table 5-3). Other rates were estimated according to case-fatality rates by age adopted by the Institute of Medicine 1986.

a. Mortality rates (per 1,000 children) estimated according to the Institute of Medicine's (1986) case-fatality ratios are as follows: Latin America, 9.8; Sub-Saharan Africa, 8.8; North Africa, 5.4; Asia, 5.2.

Source: Unpublished World Health Organization data. Ratios were calculated by the authors.

are all lower than the 6 per 1,000 estimated by Snyder and Merson (1982) from data collected before 1980.

In summary, therefore, there is evidence of a fall in diarrheal mortality rates in children in recent years, but little evidence of a parallel fall in incidence rates. This implies, on the one hand, falling case-fatality rates and, on the other, stagnating levels of the key risk factors for diarrhea morbidity. Central questions for policy that emerge are, first, to what extent the declining case-fatality rates have been created by the interventions of national CDD programs and, second, whether there are reasonable prospects for reducing morbidity over the next decade. We return to these questions later in this chapter.

Likely Morbidity and Mortality Patterns—Next Century

Although risk factors for diarrhea morbidity and mortality have been identified, and in some cases quantified, and the effects of certain interventions to control diarrheal diseases measured, only very general predictions of the likely future pattern of diarrheal morbidity and mortality are possible. In the first place, explorations of many of the relationships between risk factors and diarrhea outcome have been conducted at a relatively simplistic level—ignoring, for example, interactions between various causes—and in relatively few locations. Second, it is not clear how or how much various factors influencing diarrhea morbidity or mortality will change in the future. Evidence of past trends suggests, although only weakly, that morbidity levels have remained stagnant over the last fifteen years (see previous section), despite changes at the global level in several of the risk factors, such as substantial increases in measles immunization coverage and more modest increases in the proportion of households having improved water supply and sanitation. These global trends, however, disguise what are probably considerable variations within regions and countries, and not all these risk factors have moved in a direction associated with reductions in diarrhea rates. For example, breastfeeding rates in rural areas in developing countries have tended to decline and are unlikely to have increased significantly during the period in urban areas (Popkin and Bisgrove 1988), and nutritional status has remained stagnant in many countries, especially in Sub-Saharan Africa (Ashworth and Dowler 1991).

Nevertheless, diarrheal mortality rates in children have fallen in the last fifteen years. In the same period, overall infant and child mortality rates have also fallen throughout the developing world for reasons that are not entirely understood (Feachem, Timaeus, and Graham 1989). It is not clear how much of the diarrhea mortality decline has been brought about by increased use of oral rehydration therapy (ORT); how much by general improvement, access to, and quality of health care services at the periphery; and how much by nonspecific factors such as improving parental education (leading to more prompt attention to worsening symptoms of a sick child).

Present coverage rates and estimated use rates suggest that there is potential for mortality to decline through more effective delivery of CDD programs. Although global access to oral rehydration salts (ORS) has increased from less than 10 percent in 1982 to 51 percent in 1985 (WHO 1988c) and to 63 percent in 1989 (WHO 1991), nearly 40 percent of the population remain uncovered. The level of mortality decrease that can be expected from expanding ORT programs will depend on the risk of diarrheal death from dehydration among those as yet without access to ORS and on the potential for improvement in the quality of case management required to make a difference. Boosting coverage from current levels and, even more so, improving the correctness of ORT use, may be difficult. The CDD program has recently instituted a new applied research initiative to deal with these issues and has intensified efforts to train health care providers (doctors, nurses, paramedical staff, pharmacists, traditional healers) in diarrhea case management (WHO 1989). This will require, nevertheless, that governments or agencies be prepared to devote the necessary financial and manpower resources for it.

Improvement in the rates of use of ORT is unlikely to reduce mortality due to persistent or dysenteric diarrhea. Better overall case management is necessary and may require new methods, with special attention to feeding during the episode and recovery. The same points apply to complicated diarrheas, such as diarrheas accompanied by measles, acute respiratory infections, or malaria. These complicated diarrheas represent a considerable proportion of all inpatient diarrhea cases in some hospitals; the more so since the establishment of ORT-based outpatient facilities for the treatment of uncomplicated acute watery diarrheas.

Summary of the Public Health Significance of Diarrhea

Despite developments in the last decades in the understanding of the etiology and pathogenesis of diarrheal diseases and the discovery of an effective oral rehydration solution to treat the majority of the patients with watery diarrhea, morbidity rates among young children are still high, and diarrhea remains a significant cause of adult illness. In 1985, nearly 3 billion diarrheal episodes are estimated to have occurred in the developing world, leading to the death of 5 million persons, 80 percent of them under five years of age (see Lopez, chapter 2, this collection). Although evidence exists of a reduction in diarrheal mortality during the past fifteen years, no indication has been found of reductions in diarrheal incidence during the same period. This lack of decline points to the need for the development, implementation, and evaluation of effective measures to lower diarrheal morbidity.

Lowering Disease Incidence

The promotion of ORT for the case management of acute diarrheal diseases may have contributed to the reduction of diarrheal mortality rates observed in developing countries in the last fifteen years. Still, ORT cannot be expected to have a significant effect on the incidence of diarrhea. If morbidity rates are to be reduced, primary preventive strategies must be identified and implemented.

Elements of a Preventive Strategy

A systematic study of interventions, excluding case management, that might play a role in diarrhea control was initiated in 1982 by the Diarrhoeal Diseases Control Programme of WHO (Feachem, Hogan, and Merson 1983). Eighteen interventions were evaluated, with particular emphasis on their effectiveness and feasibility (table 5-5). Of these, four interventions—improving lactation, supplementary feeding programs, chemoprophylaxis, fly control—were found to be either ineffective or too costly for incorporation in programs of diarrheal diseases control in developing countries. Seven other interventions—prevention of low birth weight, use of growth charts, increase in child spacing, vitamin A supplementation, improvement of food hygiene, control of zoonotic reservoirs, epidemic control—were considered of uncertain effectiveness, feasibility, or cost and required further research before their potential role could be properly assessed. Two of these potential interventions—increase in child spacing and control of zoonotic reservoirs—are still under review.

Seven interventions were identified for which evidence of adequate effectiveness and feasibility were reasonably strong:

- Promotion of breastfeeding
- Improvement in weaning practices
- Rotavirus immunization (when an effective vaccine becomes available)
- Cholera immunization (in selected countries, when a more effective new vaccine becomes available)
- Measles immunization
- Improvement of water supply and sanitation facilities
- Promotion of personal and domestic hygiene

These interventions, except for improved water and sanitation, were the object of more detailed analysis of cost-effectiveness (Phillips, Feachem, and Mills 1987). Information regarding the potential effectiveness and cost-effectiveness of these interventions is summarized in table 5-6.

PROMOTION OF BREASTFEEDING. The hypothesis that breastfed infants may have a reduced risk of diarrheal morbidity and mortality is supported by evidence indicating the immunological and antimicrobial properties of breast milk, its contribution to good nutritional status during the first few months of life, and the risk associated with contaminated feeds. The literature on the risks of diarrheal morbidity and mortality among children, according to mode of feeding, was reviewed by Feachem and Koblinsky (1984). More recent studies, in which confounding was carefully controlled, have shown even higher relative risks of severe diarrhea and diarrhea mortality associ-

Table 5-5. Potential Nonclinical Interventions for Control of Diarrhea among Young Children

Strategy	*Intervention*	*Reference*[a]
Maternal Health	Preventing low birth weight	Ashworth and Feachem 1985[b]
	Improving Lactation	Ashworth and Feachem 1985[a]
Child health	Promoting breastfeeding	Feachem and Koblinsky 1984
	Improving weaning practices	Ashworth and Feachem 1985[c]
	Supplementary feeding programs	Feachem 1983
	Using growth charts	Ashworth and Feachem 1986
	Increasing child spacing	n.a.
	Vitamin A supplementation	Feachem 1987
Immunization and chemoprophylaxis	Rotavirus immunization	de Zoysa and Feachem 1985
	Cholera immunization	de Zoysa and Feachem 1985
	Measles immunization	Feachem and Koblinsky 1983
	Chemoprophylaxis	de Zoysa and Feachem 1985
Interrupting transmission	Improving water supply and sanitation facilities	Esrey, Feachem, and Hughes, 1985
	Promoting personal and domestic hygiene	Feachem 1984
	Improving food hygiene	Esrey and Feachem 1989
	Controlling zoonotic reservoirs	n.a.
	Controlling flies	Esrey 1991
Epidemic control	Epidemic surveillance, investigation, and control	n.a.

n.a. Not applicable.

Note: The general rational for the review series is described in Feachem, Hogan, and Merson, 1983. Policy conclusions are discussed in Feachem, 1986. Cost-effectiveness analysis of selected interventions is presented in Phillips, Feachem, and Mills, 1987.

a. Some of these publications are also available in French and Spanish.

Source: See table (last column) and note above.

ated with nonbreastfeeding. For example, in Basrah, Iraq, for the nonbreastfed infant the risk of hospitalized diarrhea was thirty-seven times greater than for the exclusively breastfed infant in the first three months of life and twenty-four times greater in the second three months (Mahmood, Feachem, and Huttly 1989). In Brazil in 1985, the risk of diarrheal mortality was found to be fourteen times greater for nonbreastfed infants than for exclusively breastfed infants in the first year of life. The risk of infant mortality was highest among the nonbreastfed during the first two months of life, being twenty-three times greater than among the exclusively breastfed (Victora and others 1987). No evidence could be found by Feachem and Koblinsky (1984) that indicated that protection against diarrhea extended after the termination of breastfeeding (a conclusion supported by Mahmood, Feachem, and Huttly 1989) or after the first year of life. Recent studies have suggested, however, significant protection from breastfeeding against the severity of diarrhea even during the third year of life (Briend, Wojtyniak, and Rowland 1988; Clemens and others 1986).

Breastfeeding promotion projects have been shown to be effective in increasing the number of women initiating breastfeeding and the total duration of exclusive or partial breastfeeding (Hardy and others 1982; Huffman and Combest 1988; Winikoff and Baer 1980). Methods of breastfeeding promotion have included the training and education of health professionals; the changing of hospital practices to facilitate early suckling following birth, rooming-in, limited supplementary and glucose-water feeds, and restrictions on the distribution of formula samples; and the provision of assistance to breastfeeding support groups. Large-scale projects in Brazil, Honduras, Indonesia, Panama, and Thailand were reviewed by Huffman and Combest (1988). Although few adequately designed evaluations have been carried out, the results point consistently to the success of these promotional programs in decreasing rates of nonbreastfeeding.

Theoretical calculations based on the above data (Feachem and Koblinsky 1984) indicate that promotion of breastfeeding can reduce diarrhea morbidity by 8 to 20 percent in the first six months of life and by 1 to 4 percent for children under five

Table 5-6. Effectiveness and Cost-Effectiveness of Interventions for Diarrhea Control among Young Children

Strategy	*Intervention*	*Effectiveness*[a] *(percent)*	*Cost-effectiveness*[b] *range (median) (1982 U.S. dollars)*	
Child health	Promoting breastfeeding	Reduction in nonbreastfeeding 0–2 months: 40 3–5 months: 30 6–11 months: 10	—	
		Reduction in diarrhea morbidity 0–6 months: 8–20 0–59 months: 1–4	10–75	45
		Reduction in diarrhea mortality 0–6 months: 24–27 0–59 months: 8–9	400–10,750	1000
	Improving weaning practices	Reduction in percentage of children < 75 percent weight-for-age 6–59 months: 50 Reduction in diarrhea mortality 6–59 months: 2–12	50–2000	1070
Immunization	Rotavirus immunization[c]	Reduction in diarrhea incidence: 4	3–30	5
		Reduction in diarrhea mortality: 13	140–1400	220
	Cholera immunization[f]	Reduction in diarrhea incidence: 0.2[e]	90–1450	174
		Reduction in diarrhea mortality: 2.8[e]	1,075–16,710	2,000
	Measles immunization	Reduction in diarrhea incidence: 3	3–60	7
		Reduction in diarrhea mortality: 22	66–1,156	143
Interrupting transmission	Improving water supply and sanitation	Reduction in diarrhea incidence: 27 Reduction in diarrhea mortality: 30	No meaningful estimates; multiple benefits	
	Promoting personal and domestic hygiene	Reduction in diarrhea incidence: 14–48	5–500	10

— Not available.
a. For children from birth to age fifty-nine months, unless otherwise specified.
b. Only considers diarrhea deaths or episodes averted in children under age five years.
c. Assumes 100 percent coverage with 80 percent vaccine efficiency.
d. Assumes 100 percent coverage with 70 percent vaccine efficiency.
e. In Bangladesh.
f. Assumes 100 percent coverage with 85 percent vaccine efficiency.
Source: See table 5-5.

years. Mortality rates can be reduced by 24 to 27 percent in the first six months, and by 8 to 9 percent for children under five years. Results from more recent studies indicate that these calculations are conservative, especially with reference to the prevention of diarrheal mortality, and that breastfeeding provides greater and more extended protection against diarrheal deaths and severe diarrheal episodes, even up to the third year of life (Briend, Wojtyniak, and Rowland 1988; Clemens and others 1986; Mahmood, Feachem, and Huttly 1989; Martines 1988; Victora and others 1987).

Phillips, Feachem, and Mills (1987) constructed a range of plausible costs for a variety of different breastfeeding promotion strategies (changes in hospital routine, face-to-face education, mass media campaigns, discouragement of breastfeeding alternatives, provision of facilities for working women), using information on the characteristics of these interventions, their likely resource requirements (principally in terms of staff time), and salary estimates. Even with salaries set at a constant average level and the use of a standard input package (except for mass media campaigns), the cost per child affected varied considerably within each strategy, depending on such factors as scale (hospital size in the case of hospital-based interventions; population size in the case of mass media campaigns) and on assumptions concerning the coverage of the intervention and the degree of secondary effect. Phillips, Feachem, and Mills concluded that, with a judicious selection of interventions (excluding the relatively costly strategies involving the provision of facilities for working women), it should be possible in most countries to provide a breastfeeding promotion package for about $5 per infant exposed.[1] Using this estimate and adopting conservative estimates of effectiveness based on Feachem and Koblinsky (1984), we estimated the cost-effectiveness of breastfeeding promotion to range between $10 and $75 (median $45) per diarrheal episode averted and between $400 and $10,750 (median $1,000) per diarrheal death averted in children under five years of age.

IMPROVED WEANING PRACTICES. The hypothesis that underweight children may be predisposed to diarrhea is supported by evidence suggesting that protein-energy malnutrition causes impaired cellular (Chandra 1986) and secretory immune responses (Sirisinha and others 1975). This hypothesis is further corroborated by evidence from patients with congenital or acquired immunodeficiency syndromes, who have increased diarrheal risk (Arbo and Santos 1987). Nonspecific protective mechanisms, such as gastric acid production and intestinal mucosal renewal, may also be affected by malnutrition (Brunser and others 1968; Guiraldes and Hamilton 1981). Increased risk of diarrhea has been described in hypochlorhydric individuals (Gianella, Broitman, and Zamcheck 1973), and recovery from diarrhea may be delayed by an impaired mucosal renewal (Butzner and others 1985).

Epidemiological studies conducted in Bangladesh indicate that protein-energy malnutrition is a significant determinant of diarrhea severity and duration in infancy and childhood, but not of its incidence (Bairagi and others 1987; Black, Brown, and Becker 1984a; Chen, Huq, and Huffman 1981; Palmer and others 1976). Studies in Nigeria (Tomkins 1981), Mexico (Sepúlveda, Willet, and Muñoz 1988), and the Republic of the Sudan (Samani, Willet, and Ware 1988) suggest that malnourished children may also experience increased incidence of diarrhea. The effect of nutritional status on the severity (degree of dehydration and purging rate) of diarrhea has also been investigated in clinical studies (Black and others 1981; Black and others 1984). Diarrheal mortality has also been shown to be higher in malnourished children.

In Bangladesh, children who had diarrheal episodes and whose weight-for-age was below 65 percent of the expected were 3.7 times more likely to die during the subsequent twenty-four months than their better-nourished counterparts (Chen, Chowdhury, and Huffman 1980). In northern India, case-fatality rates in children with diarrhea were significantly greater among those who were severely malnourished (7.7 percent) than among moderately malnourished (2.2 percent) or well-nourished children (0.3 percent) (Bhan and others 1986).

Poor weaning practices can be the result of lack of access to appropriate foods. Such practices, however, also appear to derive from food taboos or ignorance and to be potentially susceptible, therefore, to education. Few weaning education programs have been evaluated in terms of improvement produced in nutritional status (Ashworth and Feachem 1985c). The information available suggests that a weaning education program can halve the proportion of children who are less than 75 percent weight-for-age, children who are likely to have a diarrheal mortality rate twice as high as other children (Ashworth and Feachem 1985c). If the effect of weaning education is manifest only during the weaning period, eighteen months to twenty-three months of age marking its upper limit, reductions in diarrhea mortality in children under five years old of 2 to 8 percent may be expected when the prevalence rates of moderate and severe malnutrition in the community, before the intervention, range from 10 to 50 percent of children. If the effect of weaning education can be extended to 59 months, and indeed a high proportion of undernutrition up to this age may be the result of failure to catch up after the weaning period, reductions of diarrheal mortality of 2 to 12 percent may be expected. According to most of the evidence available, the risk of diarrheal incidence is not likely to be reduced with improvements in the child's nutritional status, although more recent studies challenge these conclusions (Samani, Willet, and Ware 1988; Sepúlveda, Willet, and Muñoz 1988). Improvements in food hygiene resulting from weaning education are likely to increase the effect of the intervention, reducing diarrheal incidence and, possibly, the severity of episodes (Esrey and Feachem 1989).

From the few available data on the cost of implementing weaning education programs, Phillips, Feachem, and Mills (1987) found that weaning education activities have been mounted for between $0.50 and $10.00 per child benefiting, though these estimates are very sensitive to assumptions concerning the number of children benefiting and the comprehensiveness of the costings. The cost to the family, in the form of purchase and preparation of food, which may be substantial, is not included in these estimates. Using effectiveness data from Ashworth and Feachem (1985c), the cost-effectiveness of weaning education was estimated to range between $50 and $2,000 per diarrhea death averted, with a median estimate of $1,070.

ROTAVIRUS IMMUNIZATION. Rotavirus is the most frequent etiological agent isolated in children under two years who attend treatment centers for diarrheal diseases in developing countries (Black and others 1980; Levine and others 1986; Mata and others 1983; Stoll and others 1982). Rotavirus vaccines can thus be expected to have a role in reducing diarrheal incidence and mortality among young children in the developing world (de Zoysa and Feachem 1985b).

No vaccine is currently available for full-scale application. Attempts are under way to develop live, attenuated, oral vaccines against disease caused by human rotavirus (Flores and Kapikian 1989) and reassortant rotaviruses that incorporate in an animal rotavirus a gene segment encoding for the VP7 surface antigen of human rotavirus serotypes 1, 2, and 4. More recently, the naturally attenuated human "nursery strain" rotavirus has also been considered for use as an oral vaccine.

Field trials conducted to date have shown that vaccination with live rotavirus vaccines, in industrial countries, can reduce the incidence of clinically significant rotavirus diarrhea by nearly 80 percent. Vaccine efficacy in developing countries, for reasons that are not fully understood, has been much lower. The level of protection against all rotavirus diarrhea has in most studies been lower than that against severe rotavirus diarrhea (de Zoysa and Vesikari 1990).

Exploring the potential of rotavirus vaccines, de Zoysa and Feachem (1985b) suggested that a rotavirus vaccine of 80 percent efficacy given to children whose average age at full vaccination was six months could achieve reductions of 4 percent in diarrheal incidence and 13 percent in diarrheal deaths among children under five.

On the basis of actual cost data available for several national vaccination programs conducted in nine developing countries, and taking into account various features of the vaccines used in those programs (whether orally administered or injected, with another vaccine at the same visit or in the same injection, and the number of doses), Phillips, Feachem, and Mills (1987) calculated an average cost per "injected dose equivalent." They then applied this cost unit to the rotavirus vaccine (as well as to the measles and cholera vaccines discussed in the following sections). Taking account of the relevant characteristics of that vaccine and assuming the presence of an ongoing vaccination program, they derived estimated costs per child fully vaccinated of between $1.20 and $12.00, with a median of $1.90. Employing effectiveness results presented by de Zoysa and Feachem (1985b), they calculated the cost per diarrhea episode averted in children under five to lie in the range $3 to $30 (median $5) and the cost per diarrheal death averted to be between $140 and $1,400 (median $220).

CHOLERA IMMUNIZATION. Intestinal infections with *Vibrio cholerae* 01 are associated with especially severe diarrheal disease that occurs in both epidemic and endemic form (Feachem 1981; Miller, Feachem, and Draser 1984). In recent years, strains resistant to multiple antibiotics have been described in Bangladesh and East Africa.

The cholera vaccines that are available at present need to be given parenterally and are of low efficacy (WHO 1986c). Current research on cholera vaccines is directed toward the development of an effective oral vaccine that uses either nonliving bacteria and purified bacterial antigens or living avirulent mutants or genetically engineered strains. The hope is that these will stimulate the substantial immunity that is known to follow clinical cholera (WHO 1986c). Field trials of new nonliving oral vaccines in Bangladesh indicated overall protection for three years of 50 percent—but only 23 to 26 percent protection for children under six years (WHO 1989). The field is controversial and fast moving, and it remains unclear which type of vaccine for widespread application will emerge from the field trials (Levine 1989).

The administration schedule for the new cholera vaccines is still tentative. Two or three oral doses in the second year of life is one possible schedule. The vaccine is likely to be administered at a new contact and at an age when healthy children are not normally brought to health services, which may increase costs and decrease coverage. De Zoysa and Feachem (1985b) investigated the potential of cholera vaccination in Bangladesh, which has relatively high rates of endemic cholera. For a cholera vaccine of 70 percent efficacy and an average age at full vaccination of two years, 0.21 percent of diarrhea episodes and 2.8 percent of diarrheal deaths in vaccinated children under five years could be averted. In countries that had a lower proportion of diarrhea episodes and deaths caused by cholera, the effects would be less.

Phillips, Feachem, and Mills (1987) calculated costs using the methodology described for rotavirus and assuming a vaccination schedule of three doses given in the second year of life, a constant dropout rate between each contact of 10 percent, and a vaccine cost per dose similar to that of measles ($0.20). The results suggested that the cost per child fully vaccinated with a new oral cholera vaccine would range from $1.70 to $27.00, with a median value of $3.20. The cost per diarrhea episode and diarrhea death averted through cholera vaccinations, assuming 70 percent efficacy of the vaccine and cost of $4.00 per child fully vaccinated, was calculated to be $174.00 per diarrhea episode and $2,000.00 per diarrhea death averted in children under five years of age in Bangladesh. This estimate, however, relates only to routinely administered vaccination and not to vaccination in the presence of epidemics, when the cost-effectiveness would probably improve. The cost of vaccination is the highest of the vaccines evaluated, possibly twice as expensive as rotavirus or measles. The relatively poor performance of cholera vaccination in terms of cost-effectiveness is largely attributable to the rarity of the disease. Cholera constitutes a small proportion of the total diarrheal cases, even in Bangladesh, and even with equal costs per child vaccinated its cost-effectiveness would be about five times lower than that of measles or rotavirus vaccines.

MEASLES IMMUNIZATION. A marked association between measles and diarrhea has been described in developing countries (Koster and others 1981; Morley, Woodland, and Martin 1963; Scrimshaw and others 1966), and measles immunization has been considered a potential intervention for diarrhea control (Feachem and Koblinsky 1983). It is the only one of the three vaccines discussed here that is already commercially available and widely used. A single injected dose at the age of nine months is recommended in most developing countries. This is an age at which children are likely to be brought to the health services for various reasons, though no other vaccines are scheduled for this age.

Feachem and Koblinsky (1983), on the basis of the proportion of diarrheal episodes and diarrheal deaths that are measles-associated and the proportion of measles cases averted in the first five years of life by measles immunization, suggest that a measles vaccine that is 85 percent efficacious, given at the age of nine months through eleven months, with coverage of between 45 and 90 percent, can prevent 44 to 64 percent of measles cases, 0.6 to 3.8 percent of diarrheal episodes, and 6 to 26 percent of diarrheal deaths among children under five years of age. This estimate may be too conservative, however, as indicated by recently reported reductions of over 80 percent in total mortality among children nine months through thirty-nine months in Haiti (Holt and others 1990) and of 59 percent in diarrheal mortality among vaccinated children age ten months to sixty months in Bangladesh (Clemens and others 1988).

Phillips, Feachem, and Mills (1987) estimated the cost per child vaccinated against measles to range from $0.60 (Indonesia, mixed strategy: static/mobile delivery) to $12.00 (Ghana, outreach delivery strategy), with a median of $1.40. The cost per diarrheal episode averted in children under five through measles vaccination was calculated as $7.00, and the cost per diarrheal death averted as $143.00. Discounting diarrhea episodes and deaths averted in years following vaccination makes relatively little difference to the results, because the primary effect of the vaccine on diarrhea in children under five occurs within two years of vaccination. These values are roughly similar to that of rotavirus vaccine, which is more cost-effective in terms of diarrheal morbidity but less cost-effective in terms of diarrheal mortality.

IMPROVED WATER SUPPLY AND SANITATION FACILITIES. All major infectious agents that cause diarrhea are transmitted by the fecal-oral route. These enteric pathogens can be transmitted via contaminated water, and water-borne transmission has been documented for most of them. Improvement in water quality is, therefore, a potentially important intervention. Improvement in water quantity and availability is also important as an aid to hygienic practices which may interrupt the fecal-oral transmission. As all principal infectious agents of diarrhea are shed by infected persons via the feces, hygienic disposal of excreta has the potential to play a role in controlling their transmission. Environmental improvements of these kinds probably contributed to the reduction in diarrheal morbidity and to the control of epidemic cholera and typhoid in Europe and North America between 1860 and 1920.

A review of sixty-seven studies from twenty-eight countries on the effect of water supply and sanitation on diarrhea, related infections, nutritional status, and mortality was conducted by Esrey, Feachem, and Hughes (1985). A median reduction of 27 percent in diarrhea morbidity and 30 percent in diarrheal mortality with the provision of improved water supply and excreta disposal was found in a subset of studies selected for their better design. Improvements in water quality appeared to have a lower effect than improvements in water availability or excreta disposal. No adequate data could be located, however, on the effect of improvements in water quality and availability together with excreta disposal. It is possible that well-designed projects combining water supply, excreta disposal, and hygiene education may achieve reductions of 35 to 50 percent in diarrheal morbidity (Esrey, Feachem, and Hughes 1985). It is expected that, except in areas where other interventions have substantially reduced diarrheal mortality, the effect will be larger on mortality rates than on morbidity.

A recent case-control study in the south of Brazil found that those infants whose homes had piped water had a diarrhea mortality rate 80 percent lower than those from homes with no easy access to piped water. No difference in mortality rates was detected, however, between infants receiving treated or untreated water, suggesting that beneficial effects of piped water may be related to the easy availability rather than its quality (Victora and others 1988). In addition to this Brazilian study, roughly a dozen studies of the effect of water and sanitation on diarrhea have been conducted since the review by Esrey, Feachem, and Hughes (1985). They were conducted in Bangladesh, the Gambia, Lesotho, Malawi, Nicaragua, Nigeria, the Philippines, and Sri Lanka. Half of them employed a case-control methodology. The studies have been reviewed recently by Cairncross (1990) and Huttly (1990).

Analysis of cost data from eighty-seven developing countries suggests median annual costs of $14 per capita for rural water supply and latrine projects and $46 per capita for a combination of in-house water supply and sewerage in an urban area (Esrey, Feachem, and Hughes 1985). The multiple benefits deriving from water-supply and sanitation interventions, including the reduction of diarrheal morbidity and mortality in other age groups, the reduction of the incidence of other infections, and other benefits not directly related to health (Briscoe 1984), make interpretation of simple cost per diarrhea death or episode averted problematic (Okun 1988). Further studies on ways to overcome these analytical difficulties are needed.

IMPROVED DOMESTIC AND PERSONAL HYGIENE. Poor personal hygiene of food handlers, inadequate cooking, and storage of food at incorrect temperatures for long periods are the most common contributing factors to food-borne diarrheal outbreaks in industrial countries (Frank and Barnhart 1986). Similar factors probably apply to food contamination in developing countries, where personal hygiene is likely to be markedly impaired by restricted water availability, overcrowding, and poor sanitation. Shortages of fuel, heavy workloads, and lack of access to refrigerators are probably additional contributory factors in developing countries (Esrey and Feachem 1989).

Unclean living conditions have been found to be associated with an increased risk of diarrheal incidence in children and adults (Bertrand and Walmus 1983; Huttly and others 1987; Taylor and others 1986). Infant-feeding bottles and bottle nipples are often highly contaminated (Elegbe and others 1982; Hibbert and Golden 1981; Phillips and others 1969; Surjono and others 1980), especially in lower-income households (Mathur and Reddy 1983). Feeding bowls and other feeding utensils have been found contaminated with *Escherichia coli* (Rowland, Barrell, and Whitehead 1978). Storage of food at high ambient temperatures increases the risk of contamination with fecal organisms (Barrell and Rowland 1979, 1980; Black and others 1982; Capparelli and Mata 1975). In these conditions, bacterial counts increase substantially with length of storage (Black and others 1982; Rowland, Barrell, and Whitehead 1978).

Few studies have been found that quantify the effectiveness of hygiene education interventions on diarrheal morbidity. Those that have been located (Bartlett and others 1985; Black and others 1981; Khan 1982; Stanton and Clemens 1987a; Torun 1982) focus mainly on the promotion of handwashing. Reductions of diarrheal incidence ranged from 14 to 48 percent, suggesting that hygiene education, and handwashing promotion in particular, has a marked effect on diarrheal rates.

Information on the cost of hygiene education is scarce. Costs are lower than for the provision of water supply and excreta disposal facilities, but the success of the promotion of handwashing may depend on the presence of these improved facilities (Feachem 1984). Analysis of three educational interventions for which data are available reveals a range of cost-effectiveness of under $20 per childhood case averted for village-based group education and supervision of day-care centers, to $300 to $500 per case averted for individual education of families presenting one or more cases of shigellosis (Phillips, Feachem, and Mills 1987).

Development of a Preventive Strategy in the Next Decade

During the next decade, the mainstay of diarrhea prevention will probably continue to be the interventions discussed above and listed in table 5-6. The change that can be expected is in the effectiveness (and the cost-effectiveness) of these interventions. The goal pursued in the use of the interventions, except for the immunizations, is substantial behavior change through education. Public health education is a relatively new field, and most countries currently lack the ability to deliver health education messages effectively to appropriate target groups. As experience grows and technology improves, these antidiarrhea programs can be expected to yield greater benefits. The emphasis on education in the current AIDS-control strategy can only accelerate this process. The only new interventions that are expected are new vaccines. The next decade may see the incorporation into immunization programs of new vaccines against *Escherichia coli* and *Shigella*, besides the vaccines against *Vibrio cholerae* and rotavirus that were reviewed earlier in the chapter.

ESCHERICHIA COLI VACCINES. The incidence of diarrhea associated with enterotoxigenic *E. coli* in developing countries appears to be highest in children under two years, in which one or even two episodes per year have been noted. The incidence remains high in older children. Because partial immunity appears to develop after childhood, the target population for vaccination would be children during the first six months of life. It is difficult to estimate the number of strains the vaccine would need to cover, and a small proportion of disease would still occur at an early age, before vaccination could confer full protection.

Taking these two factors into account, the U.S. Institute of Medicine (1986) estimated that 50 to 60 percent of enterotoxigenic *E. coli* episodes would be vaccine preventable. Recent advances in the development of vaccines against diarrhea due to enterotoxigenic *E. coli* were reviewed by Levine (1989, 1990). The first experimental vaccines were expected to be ready for testing in human volunteers in 1990 (WHO 1989). Studies in Swedish volunteers have shown that the prototype *E. coli* vaccine is safe and immunogenic. At least 80 percent of the volunteers developed intestinal antibody response to the antigens after receiving two or three doses of vaccine. (WHO 1992)

SHIGELLA VACCINES.The development of effective *Shigella* vaccines deserves special priority. Of all the diarrhea-causing agents, it is the most life-threatening. *S. dysenteriae* is responsible for an especially serious form of dysentery which can prove difficult to manage, even in sophisticated clinical settings. Major outbreaks of drug-resistent *S. dysenteriae* have occurred in the past thirty years in Central America, Central Africa, and Bengal (East and West) and have resulted in hundreds of thousands of deaths in all age groups. Nalidixic acid was the antibiotic of choice in these circumstances, but resistance to this product is now reported.

The incidence of shigellosis in developing countries is highest for children age two to four years, but it is already a problem from six months of age. All age groups are susceptible and could benefit from immunization. A vaccine incorporating protective antigens from the most common infecting strains in a given geographic area should prevent 80 to 90 percent of the *Shigella* infections, depending on the prevalence of these strains and assuming total coverage of the target population with a vaccine that is 100 percent effective and is delivered at the earliest feasible age (U.S. Institute of Medicine 1986). *Shigella* vaccines are reviewed by Levine (1989). A candidate vaccine, developed from a live attenuated *S. flexneri* strain, is being tested for safety and immunogeneity in the United States. Other efforts are under way in France and Sweden (WHO 1989).

Ideal Prevention and Current Prevention: Closing the Gaps

The following section describes the technical and institutional aspects involved in closing the gap between current preventive practices and ideal prevention.

TECHNICAL ASPECTS. Although a set of behaviors associated with lower diarrheal incidence and reduction of severity has already been identified, there is still a long way to go before these desirable behaviors are widespread and commonplace and before the necessary improvements in water, sanitation, and kitchen equipment are available to most families. Exclusive breastfeeding during the first four to six months of life, followed by partial breastfeeding during the remainder of the first year of life, can be expected to reduce infant diarrheal morbidity and mortality significantly. Trends in developing countries have, however, been toward lower prevalence and duration of breastfeeding in urban areas (Popkin, Bilsborrow, and Akin 1982; Popkin and Bisgrove 1988), and early food supplementation for breastfed infants is the rule, rather than the exception. Early weaning and inadequate supplementation, the use of foods of low energy and nutrient concentration, the selection of single foods of low nutritional value, the use of contaminated foods, feeding at infrequent intervals, and giving infants a disproportionately small share of the family food are still common practices in developing countries (Ashworth and Feachem 1985c).

Measles vaccination should reduce diarrheal mortality in children under five. Coverage, however, remains low in some regions, averaging 46 percent in Africa and 51 percent in Southeast Asia (WHO 1990a), and the effectiveness of vaccines may be reduced by an inadequate "cold chain." Improvements in water supply and sanitation can lead to reductions in diarrheal morbidity and mortality in children under five of about 30 percent. Access to better facilities does not imply improved use, however, and water and sanitation interventions have failed to reduce diarrheal rates in some settings (Nigeria, Imo State Evaluation Team 1989; Ryder, Reeves, and Sack 1985). Personal and domestic hygiene behaviors that may reduce diarrheal incidence have been identified. Handwashing before preparing and offering food and careful disposal of child feces, two potentially effective practices, may depend on changes in attitudes and in the availability of water and soap. In Bangladesh, for example, it was observed that mothers washed their own hands before offering food to young children in 53 percent of feedings but in almost all cases without using soap. Other caretakers were observed washing their hands when offering the food in only 11 percent of the feeds (Guldan 1988).

INSTITUTIONAL ASPECTS. The WHO/CDD program has played a major role since 1980 in promoting research on diarrhea epidemiology, vaccine development, and the cost-effectiveness of specific interventions. Much of the work reported in this chapter on diarrhea prevention has been initiated or influenced by WHO/CDD. It is important that this effort continue with an increased focus on research that will assist in the design and delivery of cost-effective interventions.

The WHO/CDD program is taking substantial steps to influence the ability and commitment of governments to implement these known effective interventions. Measles immunization and improvements in water supplies and sanitation are under way in any case and are not the responsibility of national CDD programs. The other interventions discussed here (table 5-6) exist in a very limited fashion in most countries. A great challenge for the WHO/CDD program during the next decade lies in rectifying this situation. Promotion of exclusive breastfeeding in the first four to six months of life is the first preventive intervention chosen by WHO/CDD for implementation efforts, which started in 1990.

Defining the Optimal Preventive Strategy

What preventive measures should reasonably be taken for any particular population will depend on a range of factors—the relative and absolute importance of diarrhea morbidity and mortality; the relative importance of different etiologies and of the risk factors that predispose children and adults to diarrhea; the nature and extent of the existing infrastructure; government priorities for development and ongoing interventions; relative and absolute price levels; and, very important, the level of relevant budgetary constraints.

Several of the preventive strategies, in addition to being relatively cost-effective in preventing diarrhea (still one of the most important causes of death in many developing countries), have important additional potential health benefits beyond diarrhea control. It would seem reasonable, therefore, that at least one-twentieth of a country's health budget be spent on efforts to prevent diarrhea—say $1 per head for high-mortality countries (whose health budgets are generally small) and $3 per head for lower-mortality (and generally higher-income) countries. A rough order of priorities for preventive interventions, based substantially on the cost-effectiveness of currently available technology, is set out below:

- Measles vaccination for at least 80 percent of the nine-to twelve-month-old population. At a cost of about $2.00 per additional child vaccinated (assuming a vaccination program is already in place), and possibly double that to cover the least accessible final 20 percent, this amounts to some $0.10 per head, or up to 10 percent of the proposed budget allocation for diarrhea prevention in high-mortality countries. Such a vaccination program would be expected to avert 23 percent to 29 percent of diarrheal deaths in those under five years of age. It would also avert substantial measles mortality and, in areas where measles is severe and associated with high risks of xerophthalmia, an additional benefit would be the prevention of a substantial proportion of blindness.

- For areas where breastfeeding rates are low or early supplementation is a common practice, investment in breastfeeding promotion aimed at achieving exclusive breastfeeding up to four or six months should also be a priority. Some interventions, such as changing hospital routines, can be implemented relatively cheaply (under $1.00 per delivery—or less than $0.05 per head even if all children were delivered in a hospital and routines changed in all hospitals). For about $0.20 per head per year it should be possible to implement a package of hospital-based, legislative, and mass media measures designed to improve breastfeeding rates.
- With the remaining funds available, promotion of improved weaning and hygiene practices for mothers (both feasible for about $0.30 per head each), should be next on the agenda (the former particularly for high-mortality countries), although adoption of hygiene practices may be constrained by water availability.
- Improvements in water and sanitation facilities are relatively expensive, estimated at between $14 to $46 per head annually. Even if the whole of the $1 to $3 per head notionally set aside for diarrhea prevention were allocated to water supply, only one-fifth to one-forty-fifth of individuals would be covered by the interventions. Some countries could partially overcome this difficulty by requiring that individual consumers be responsible for some or all of the costs of these services, which they may, indeed, provide for themselves. Self-provision of Ventilated Improved Pit latrines in Lesotho is a case in point and has achieved notable health benefits (Daniels and others 1990).

Case Management

The elements of the current case management strategy, its likely development over the next decade, the gap between good and actual case management, and the definition of an optimal case management strategy are examined in this section.

Elements of a Case Management Strategy

Case management involves several dimensions: the way diagnoses are made, the nature of medication and advice offered, and the level and location of services. We concentrate principally on the effectiveness and costs of medication options, referring more briefly to the way these are influenced by various options for making diagnoses and for providing services.

A serious complication of some diarrhea episodes is dehydration, which can lead to death, particularly in small children. Correct case management involves, at a minimum, the prevention and correction of dehydration. Considerable effort has been devoted in the last twenty years to the development and promotion of rehydration solutions which can be taken orally. These advances, and the effectiveness and cost of the alternative methods of prevention and correction of dehydration, are outlined below. We follow this with a discussion of antibiotics and antidiarrheals and their limited role in curative and palliative treatment of diarrhea.

SECONDARY PREVENTION: REHYDRATION. Until the late 1960s the primary medical method of rehydration was intravenous (IV) therapy. The development of oral rehydration solutions, combining electrolytes and glucose, sucrose, or rice powder, has been an important breakthrough (Darrow and others 1949; Nalin and others 1968; Pierce and others 1968; *Lancet* 1981). The composition for ORS recommended currently by WHO is 3.5 grams of sodium chloride, 2.9 grams of trisodium citrate dihydrate, 1.5 grams of potassium chloride, and 20 grams of glucose (WHO 1987c). Clinical studies have shown that ORS can successfully rehydrate 90 to 95 percent of cases of acute watery diarrhea, substantially reducing the requirements for IV rehydration (Hirschhorn 1980; Levine and others 1986). Not only are ORS as effective as intravenous rehydration in the vast majority of cases, they are also less hazardous, especially in settings in which the risk of infection in the hospital is high.

In efforts to identify ways of promoting early and increased use of rehydration therapy, researchers have explored the efficacy of fluids which can be prepared with ingredients available in the home. Solutions of sugar and salt (SSS) have been shown to correct fluid volume deficits in noncholera diarrhea in adults and children (Clements and others 1981; Islam and others 1980). They correct acidosis slowly, however, and are not adequate for the correction of hypokalemia or the replacement of electrolyte losses in cholera (Islam and Bardhan 1985). Home-based fluids (such as gruels, soups, and diluted yoghurt drinks) which contain some salt and a source of glucose, can be effective in preventing dehydration as long as the sodium concentration lies in the range of 30 to 80 millimolars, and the osmolarity is less than 300 milliosmoles per kilogram of water (WHO 1987a). The glucose range is not relevant if a complex carbohydrate is used.

Studies of the effectiveness of ORT promotion under field conditions are not uniformly positive in their findings (for example, Tekce 1982). This is small wonder, given the reliance on adequate supplies of ORS and the multiple steps required by caretakers in the preparation and use of ORT, where practice can readily stray from the ideal. In a later section we provide some evidence of the extent to which practice diverges from the ideal. Nevertheless, the overall findings on effectiveness tend to be positive. Studies in Egypt (Kielman and others 1985) and India (Kielman and McCord 1977) described marked decreases in diarrhea-associated mortality rates with the use of SSS by village health workers for the treatment of diarrhea. It is not clear, however, if the results were due to the use of SSS at home, an increase in the use of ORS in the treatment of more severe cases, or the repeated home visits by health workers. Recent evaluations of the effect of oral rehydration therapy in Egypt associate a sharp reduction in diarrheal mortality rates among children under five with improved diarrheal case management by mothers and doctors (Egypt, National Control of Diarrheal Diseases Project 1988; el-Rafie and others 1990). The constancy of death rates from other causes, the nature of the change in the seasonal pattern of total mortality, and the lack of change in diarrhea incidence or nutritional status are all compatible with the hypothesis that improved case management is the explanation for the reduction in diarrhea mortality. Nevertheless, uncertainty as to the accuracy of mortality statistics may indicate a need for caution in the evaluation of these results.

Data on the effect of ORT in a hospital setting summarized by WHO/CDD from twenty-eight reports from twenty-one countries indicate median reductions of 61 percent in diarrhea admission rates, 71 percent in overall diarrhea case-fatality rates, and 41 percent in inpatient diarrhea case-fatality rates. Reductions of nearly 70 percent in the proportion of hospitalized cases treated with IV fluids after the introduction of ORT were reported from Malawi and Tanzania. In Stanley Hospital, Madras, India, the average number of days of hospital stay decreased from 6 to 1.5 in association with the gradual increase of ORT use in a period of seven years (WHO 1988a). In a hospital in Haiti, for example, diarrhea mortality fell from 35 percent to 14 percent and then to less than 1 percent with the creation of an ORT unit (Allman and Rohde 1985).

The effectiveness of ORT, high in preventing death from dehydration caused by acute watery diarrheal episodes and, possibly, in aiding recovery of appetite and thus increasing food intake, is probably low in the prevention of death from persistent and dysenteric episodes.

The cost of ORS is low; UNIPAC (the central warehouse of UNICEF in Copenhagen) provides 1-liter sachets for $0.07. A course of treatment using 2 to 3 liters would cost $0.14 to $0.21 per episode. The cost of the ingredients for home-based solutions is likely to be lower than the cost of packaged ORS, and certainly the cost is lower for the health services if ORS are otherwise supplied free or at a subsidized rate. Still, other costs to the health services may be greater when home-based solutions rather than ORS are used. The effectiveness and safety of SSS depend, for example, on the ability of mothers to learn and retain the skills required in its preparation. This calls for educational interventions which may need to be more substantial than those required for ORS. Education of mothers on the use of SSS has been shown to be short-lived in its effect on behavior (AED 1985; Chowdhury, Vaughan, and Abed 1988; WHO 1986b), which suggests the need for more effective or repeated education. How this compares with the kind of effort required to educate mothers about ORS is, however, not documented.

Oral rehydration salts and home-based fluids differ in their cost implications for families, and the net result is difficult to judge. On the one hand, ingredients for home-based fluids are likely to be fully paid for by the family, whereas ORS may well be wholly or partly subsidized. Household costs for preparing food-based fluids may be particularly high if regular preparation of small quantities (with the associated time and fuel demands) is required in order to avoid spoilage. On the other hand, if ingredients are at hand, home-based fluids may be more convenient to mothers, reducing costs in time and transportation associated with visits to health facilities. Treatment-associated household costs in using ORS could, however, be reduced by regular stocking of household or neighborhood supplies. Both ORS and home-based fluids probably place considerable time demands on mothers. Evidence is scarce, but a rough calculation suggests that a mother with young children could spend 10 percent of the year treating diarrhea in her children with ORT (Leslie 1989).

Oral rehydration therapy is considerably less costly than intravenous rehydration, not only in terms of the ingredients and equipment but, more important, because of the reduced demand for hospital beds and all the associated inpatient costs. Oral rehydration therapy can generally be provided at the lowest level of health facility or in the home, as can the clinical diagnosis required both to distinguish watery from other diarrheas and to identify the degree of severity of dehydration. At Safdargang Hospital in New Delhi, India, diarrhea treatment costs were reduced by 69 percent and at San Lazaro Hospital, Manila, the Philippines, by 62 percent, when ORT was introduced (WHO 1988c). In a children's hospital in Mexico City, the opening of an oral rehydration unit reduced the number of inpatients with diarrhea by 25 percent, giving rise to considerable potential savings, (Phillips, Kumaté-Rodrígues, and Mota-Hernández 1989). Another study in Mexico City also identified savings as a result of the introduction in two clinics of therapeutic norms stressing the importance of ORT (Castro and others 1988). In the first two years following staff training and the establishment of an ORT unit at the Kamuzu Central Hospital, Lilongwe, Malawi, there was a 50 percent decrease in the number of children admitted to the pediatric ward with diarrhea, a 56 percent decrease in the use of intravenous fluids to rehydrate such children, and a 32 percent reduction in recurrent hospital costs attributable to pediatric diarrhea (Heymann and others 1990). The results, however, are not uniformly positive. In a study in Indonesia, neither hospitalization rate nor intravenous fluid expenditure were related to the rate of ORS use in the community (Lerman, Shepard, and Cash 1985). The time demands of ORT probably remain higher than for IV rehydration, which may partly explain why in many cases children hospitalized with diarrhea who could be treated with ORT receive IV therapy instead.

Relatively few studies have attempted to measure both the costs and the effectiveness of field-based ORT programs, and with few exceptions measures of health effects (for example, deaths averted) have not been used. "Diarrhea cases treated" is the most common direct measure of effectiveness. The nature of the cost analysis in these studies has not been consistent. Shepard, Brenzel, and Nemeth (1986) identified studies with adequate cost data in only four countries and reanalyzed the cost data to generate reasonably compatible estimates of full economic costs. The results from these studies and three additional ones are shown in table 5-7 and reveal costs per child treated in the range of approximately $1 to $10. Much of the variation in cost between countries can be explained by differences in gross national product per capita. The rest is probably the result of (a) differences in the level of services provided (Horton and Claquin [1983] found an ap-

Table 5-7. Cost of Treatment with ORT

Location	*Average cost per child treated (1982 U.S. dollars)*	*Reference*
The Gambia	0.70	Shepard, Brenzel, and Nemeth, 1986
Indonesia	0.77	Shepard, Brenzel, and Nemeth, 1986
Malawi	1.86	Qualls and Robertson, 1989[a]
Honduras	2.94	Shepard, Brenzel, and Nemeth, 1986
Bangladesh	3.30	Horton and Claquin, 1983
Egypt	5.56[b]	Shepard, Brenzel, and Nemeth, 1986
Swaziland	6.28	Qualls and Robertson, 1989[a]
Turkey	9.66	Brenzel, 1987

a. Study reports data collected in 1984.
b. Cost per child in the population.
Source: See last column of table.

proximately tenfold difference in cost between treatment in basic facilities and that in relatively sophisticated facilities in Bangladesh); (b) the scale of the operation's fixed costs, which tends to be relatively high (for example, 96 percent of the Turkish ORT program costs were fixed [Brenzel 1987]), giving rise to substantial changes in average costs as the program expands; (c) the efficiency with which the program is conducted; and (d) the costing methodology employed, particularly with respect to the measurement of personnel costs, which are often the largest component and the least straightforward to measure.

The effectiveness of the programs in averting deaths is likely to vary, depending on the nature and severity of all the diarrhea cases, the degree of selectivity in treatment, how well the intervention is delivered, and the extent of use and effectiveness of alternative treatments. Case-fatality rates prior to the widespread use of ORT were estimated to be of the order of 6 per 1,000 (Snyder and Merson 1982). If ORT were 100 percent effective and targeted at the diarrhea group with a case-fatality ratio of 10 per 1,000, then deaths averted would be 1 percent of treated cases. If case-fatality ratios were higher or ORT programs were successfully targeted at those with even more severe diarrhea, then effectiveness would increase. If the pre-ORT case-fatality rates were lower, 1 per 1,000, for example, and ORT were only 50 percent effective, deaths would be averted in 0.05 percent of the treated cases. Table 5-8 shows how costs per death averted vary for different costs per episode treated and deaths averted per case treated. The range of most likely estimates appears to be between $1,000 and $10,000. Most of the estimates of Shepard, Brenzel, and Nemeth (1986) lie below $10,000, and some below $1,000.

Table 5-8. Cost per Death Averted for Different Treatment Costs and ORT Effectiveness

Costs per episode treated (U.S. dollars)	*Cases treated that prevented one death*			
	0.05	*0.10*	*0.50*	*1.00*
0.50	1,000	500	100	50
1.00	2,000	1,000	200	100
5.00	10,000	5,000	1,000	500
10.00	20,000	10,000	2,000	1,000

Source: Authors' calculations from assumptions based on figures of table 5-7.

CURE AND PALLIATIVE TREATMENT—DRUGS. A large variety of drugs is currently promoted commercially for the management of diarrhea. They include antimotility drugs, antisecretory drugs, adsorbents, and antibiotics. The majority of these drugs have no proven benefit and can be positively dangerous, particularly for small children. Most have a minimal effect on the clinically important aspects of diarrhea, some have negative side effects, and all are suspected of diverting attention away from life-saving rehydration therapies. Table 5-9 outlines the evidence on the efficacy of selected drugs commonly promoted as antidiarrheals.

Case management for adult sufferers of diarrhea poses different challenges from those of childhood diarrhea. Not only are there differences in the relative incidence of different etiologies of diarrhea and in the average severity and length of episodes (U.S. Institute of Medicine 1986) but also in the significance of different characteristics of diarrhea. For example, the inconvenience of poor control over defecation is likely to be an important motivation for adults seeking treatment for diarrhea. Furthermore, the negative side effects of antidiarrheals are generally less severe for adults. Palliative treatment, strongly discouraged for young children, given the currently available selection of drugs, has a role to play in adult treatment.

Patients with AIDS commonly suffer from severe and chronic watery diarrhea, associated variously with protozoan organisms such as *Isospora belli* and *Cryptosporidium* (Young 1987), with mycobacterial organisms such as *Mycobacterium avium intracellulare* (Carswell 1988), and occasionally with well-recognized agents such as *Giardia*, *Salmonella*, *Shigella*, and *Campylobacter*. Some reports have suggested improvements of diarrhea in patients who have been treated with either spiramycin or α-eflornithine, though the evidence is not consistent (Kaplan, Wofsy, and Volberding 1987). At the present time maintenance of hydration and, in adult patients, symptomatic control with opiate derivative antidiarrheals are the only helpful interventions (Kaplan, Wofsy, and Volberding 1987), though a role for prostaglandin inhibitors has been suggested (Young 1987).

For all ages there is a legitimate, though limited, role for antibiotics in the treatment of diarrhea: antibiotics can significantly diminish the severity and duration of diarrhea due to cholera and *Shigella* and shorten the period of pathogen excretion in the case of dysenteric episodes. Antibiotics have no proven value for the routine treatment of acute watery diarrhea, however, and their use, besides being inappropriate, may

Table 5-9. Efficacy and Side Effects of Selected Drugs Promoted for Treatment of Diarrhea

Drug	Efficacy	Side effects
Antimotility		
Loperamide (Imodium)	Trials have failed to demonstrate clinically significant effects on daily stool volume or rehydration requirements	Can prolong infectious diarrhea, cause toxic megacolon, central nervous system toxicity
Diphenoxylate (Lomotil)	No clinically important reduction in number or volume of stools, length of episode, or intravenous liquids required	Can worsen clinical course (prolong fever and Shigella excretion); central nervous system toxicity at recommended doses
Antisecretory		
Bismuth subsalicylate (Pepto–Bismol)	No effect on quantity of liquid or total stool weight; diminished number of liquid stools and subjective complaints in young adults with travelers' diarrhea	Required doses too large to be practical or safe
Aciduric bacteria	No therapeutic or prophylactic benefits demonstrated	—
Adsorbents		
Kaolin	Can increase consistency of stool; no effect on weight, liquid content, or frequency of stools	May interfere with efficacy of antibiotics
Charcoal	Ineffective	Interferes with effects of tetracycline
Attapulgite and Smectite	Can increase consistency of stools; no conclusive evidence of effect on fluid or electrolyte losses	May bind and inactivate other drugs
Cholestyramine	Conflicting evidence; not recommended	Interferes with fat and vitamin absorption

— Not available.
Source: WHO 1986 and 1990.

even be dangerous (WHO 1986a). In Basrah, for example, Mahmood and Feachem (1987) found that antibiotic therapy was significantly associated with prolonged hospitalization of infants with diarrhea caused by enteropathogenic *Escherichia coli.* In table 5-10 it is noted which antibiotics are recommended for the treatment of diarrhea associated with specific pathogens.

On grounds of efficacy alone many of the drugs marketed as antidiarrheals can be dismissed. Furthermore, they can be quite costly: a bottle of tetracycline syrup, for example, costs more than six times that of a liter-size package of ORS in Indonesia. This, together with the high rate of use of antibiotics and antidiarrheals (discussed later), accounts for the substantial levels of expenditure on these drugs. Sixty percent of drug costs for treating simple diarrhea were spent on antimicrobials in one area of Indonesia (Quick and others 1988). In another study in Indonesia (Lerman, Shepard, and Cash 1985), more than five times as much was spent on antimicrobials and antidiarrheals as on ORS ($1.01 compared with $0.18 per child).

For the relatively few cases of diarrhea in which antibiotics can appropriately be prescribed, recommendations concerning the preferred choice from the range of available drugs have largely been based on relative efficacy (taking into account the problem of resistance) and severity of side effects. Costs have

Table 5-10. Antibiotic Treatment for Specific Diarrheal Diseases

Disease	Recommended treatment	Alternatives
Cholera (proven or suspected)	Tetracycline or doxycycline	Furazolidone or sulamethoxazole-trimethoprim
Dysentery (no coproculture necessary)	Sulfamethoxazole-trimethoprim	Nalidixic acid or ampicillin
Amebiasis (trophozoite in stool)	Metronidazole	In severe cases, dehydroemetine hydrochloride
Giardia lamblia (trophozoite or giardial antigen in stool)	Metronidazole	Quinacrine
Campylobacter	Erythromycin[a]	None
Severe *Yersinia*	Chloramphenicol	None
Escherichia coli rotavirus	No antibiotics[b]	None

a. Antibiotic treatment is recommended only if rapid diagnosis is possible and treatment can begin on the first day.
b. Antibiotics can lead to harmful overgrowth of organisms such as *Clostridium difficile*, with attendant necrotizing colitis.
Source: WHO 1986c and 1990b.

not been an important consideration. That the cost of alternative regimens can be significant is illustrated by *Giardia*, for which no treatment is usually required: the cheapest recommended treatment (quinacrine) costs less than one-eighth of the most expensive recommended treatment (furazolidone) (Stevens 1986).

Laboratory tests are often used to discriminate between different etiologies of diarrhea. These tests are of very limited value for guiding therapy, however, and their costs can be high. It is claimed, for example, that routine stool culture has been one of the most costly and ineffective microbiological tests, with the costs per positive result exceeding $1,000 in the United States (Guerrant and others 1985).

REHABILITATION—CONTINUED FEEDING. Among infectious diseases, diarrhea is probably the most common contributor to malnutrition in developing countries. Malnourished children are particularly prone to more persistent and severe diarrheal episodes, and possibly they are at higher risk of frequent episodes, leading to further nutritional deterioration and allowing less time for recovery and catch-up growth. The need to prevent and offset the deterioration of the nutritional status, and the evidence that recovery is accelerated with continued feeding during diarrhea, make nutritional care of acute and persistent diarrhea episodes a key element of case management (United States, National Research Council 1985; WHO 1988b). Despite efforts at continued feeding during diarrhea episodes, the reduced food intake (due to anorexia or food withholding), malabsorption, and increased catabolism are likely to result in net nutritional losses. This leads to weight loss and growth retardation. Increased consumption is required, therefore, during convalescence to compensate for weight loss and to allow catch-up growth.

Continued feeding during the active and early convalescence phases of diarrhea has been recommended by the Subcommittee on Nutrition and Diarrheal Diseases Control of the United States National Research Council (1985). Two important objectives are addressed through continued feeding: to minimize the nutritional effect of the illness and to promote normal intestinal mucosal renewal and absorptive and digestive functions. These objectives are the same whether the treatment is being carried out in a hospital or at home. Choice of foods, modes of preparation, and frequency of feeding depend on the child's age, feeding history, and physiological status. Feeding recommendations should take into account the cultural norms and practices, food availability, economic constraints, and the difficulty of preparation of the foods in the home. Breastfeeding should be continued and, for children less than six months, breast milk alone given at adequate frequency is likely to offset the effect of diarrhea on nutritional status. For infants older than six months, breastfeeding should be continued but supplemented with other foods.

The selection of weaning foods to be recommended by health authorities should take into account the fat-to-energy ratio, the quality of the mixture of dietary proteins, and the carbohydrate content. Fat should supply 40 to 50 percent of the dietary energy during the first six months of life and 34 to 40 percent for the remainder of early childhood, lower ratios being associated with increased bulk and higher risk of inadequate energy intake. A combination of unsaturated fats and mixed long-chain saturated fats is likely to lead to better absorption than saturated fats alone. Malabsorption of fats does not appear to exacerbate diarrhea, but it does prolong nutritional rehabilitation and, if protein intake is marginal, adversely affects nitrogen retention (United States, National Research Council 1985). Animal protein is generally more digestible and of higher biological quality than plant protein. Plant proteins can be mixed, however, to improve their biological quality. Carbohydrates, mostly starches, sucrose, and lactose, usually account for 35 to 55 percent of energy intake in early infancy. Although feeding of lactose to infants with diarrhea may be considered unwise, given the recognized reduction in intestinal lactase during illness, this type of acquired lactase deficiency is seldom total. Concentrations of lactose equivalent to those found in half-strength cow's milk are generally well tolerated in diarrhea, especially in mixed foods, such as milk-cereal combinations (United States, National Research Council 1985). Sucrose and processed vegetable starches are usually easily digested and absorbed in children with diarrhea. Misconceptions concerning the significance of transient intolerance to carbohydrates too often lead to unnecessary food withholding. The risk of intolerance can be minimized by multiple feeding of small amounts of mixtures of carbohydrates. If single trials with foods that contain lactose do not aggravate clinical symptoms, continued tolerance during convalescence may be assumed (United States, National Research Council 1985).

Food preparation should take into account its energy density, consistency, digestibility, and acceptability. Energy density can be enhanced by increasing the fat content. Watery paps and soups should not comprise the entire diet, given their low energy concentrations. Meals should be small and frequent (at least once every three to four hours), especially in early treatment. During convalescence, increased intake of food (at least 25 percent higher than levels before the illness) should be ensured for more than two weeks, because early resumption of usual feeding patterns will probably be inadequate for full recovery in a reasonable period.

Case Management Strategy for the Next Decade

Case management of diarrheal diseases is likely to become more effective and to reach a greater proportion of the population in the next decade. More attention will probably be paid to the maintenance of the nutritional status of diarrheal patients, the use of improved oral rehydration solutions that will actually decrease stool losses, and the control of persistent and dysenteric episodes, possibly through the use of newly developed drugs together with adequate nutritional support.

SECONDARY PREVENTION—IMPROVED ORS. Intense research efforts have been dedicated to the development of oral rehydration solutions that might correct dehydration and decrease stool output. The basic principle is to increase intestinal sodium absorption by providing larger amounts of different types of organic carriers than those present in the glucose-based ORS. The most promising of the improved ORS formulations studied to date is rice-based ORS. Results of clinical trials performed with rice-based ORS indicate that the rate of stool loss is significantly reduced (33 to 42 percent during the first twenty-four hours of treatment) in patients with rapidly purging diarrhea who are given rice-based ORS solution, as compared with patients given glucose-ORS solution. Treatment with rice-based ORS in such patients also reduces the duration of diarrhea. These reductions in the rate of stool loss and in the duration of diarrhea combine to cause an even greater reduction in total stool output during the entire illness. Feeding rice to patients given glucose-based ORS solution does not appear to cause the same reduction in stool output as treatment with rice-based ORS solution (WHO 1990c). The results summarized above indicate that rice-based ORS can be recommended in the treatment of patients with rapidly purging diarrhea. Its role in the treatment of less severe diarrhea, however, is still unclear and is the subject of ongoing research.

CURE AND PALLIATIVE TREATMENT—NEW DRUGS. As the understanding of secretory physiology increases, new methods of controlling watery diarrhea may be developed, and both improved antibiotics in the treatment of dysenteric episodes and drugs able to reverse the derangements caused by bacterial toxins may be produced (Guerrant 1986). Advances are also to be expected in drugs that are useful in persistent diarrheas. The interested reader should refer to Kandel and Donowitz (1989) and Murray and DuPont (1989).

REHABILITATION—CONTINUED FEEDING. Increasing attention has been paid to continued feeding during diarrheal episodes as a way of reducing the negative effects of the disease on child growth and the nutritional status of adults and children. More and more evidence indicates that continued feeding has no negative effects on the severity or duration of the disease and that it significantly improves nutritional outcomes (Brown and others 1988). Lactose intolerance has been found to be a minor problem among infants older than six months (WHO 1988b). Studies are being conducted to evaluate the effectiveness and safety of lactose-containing diets for feeding young infants suffering with diarrhea.

Good and Actual Case Management: Closing the Gap

The following section describes the technical and institutional aspects involved in closing the gap between good case management and actual case management practices.

TECHNICAL ASPECTS. It is unfortunately true that the usual management of diarrhea patients is markedly at odds with recommended methods. Secondary prevention in the form of the prevention and treatment of dehydration, although acknowledged to be the crucially important element in the case management of diarrhea, is not common practice everywhere. However, antibiotic and palliative treatment is frequent, despite substantial evidence of its inefficacy and risk, particularly for children. Rehabilitation through the adoption of appropriate feeding practices following a diarrhea episode is less likely to take place among the groups at higher risk of diarrheal incidence or severity and has been promoted less strenuously than the prevention and treatment of dehydration.

Table 5-11 shows the nature of treatment provided to children under five years of age with diarrhea according to a set of WHO/CDD surveys in sixty countries. Although the median of use of some form of oral rehydration therapy was more than 50 percent of cases, ranges were very wide. "Other medicine," often indicating antibiotics or antimotility drugs, was reported to have been used in nearly 50 percent of cases. This general picture is fleshed out by more detailed studies in specific settings. In a household survey in four subdistricts in Indonesia, Lerman, Shepard, and Cash (1985) found that almost three-quarters of all episodes of diarrhea were treated with another agent, either alone or in combination with ORS (which were received by about 50 percent of the patients): 34 percent were treated with tetracycline, 27 percent with iodochlorhydroxyquin, and 23 percent with sulphaguanidine. Another study in Indonesia (Quick and others 1988) supported these general findings: antibiotics were prescribed in over 90 percent of cases, more than twice as frequently as ORS (with children under five receiving an average of five drugs per episode), and vitamins and minerals were prescribed more often than ORS. Furthermore, the antibiotics were often prescribed in inadequate quantities. There was no evidence that prescribers distinguished diarrheas benefiting from antibiotics from those worsened or unaffected by antibiotics. A study in Nepal found that despite extensive ORT education of families, only 8 percent of diarrhea patients received ORS or home fluids (Wornham 1987).

A small hospital-based study in Mexico City found that although hospital treatment was reasonably satisfactory, prehospital treatment involved very high antibiotic and antidiarrheal use (Phillips, Kumaté-Rodrígues, and Mota-Hernández 1989). A study of hospitalized infants with diarrhea in Iraq found that intravenous rehydration was given in 94 percent of cases and antibiotics in 50 percent (Mahmood and Feachem 1987). The authors judged that most of this IV and drug use was unnecessary.

Evidence from the pharmaceutical industries supports the suggestion of substantial use of largely ineffective or dangerous drugs: the antidiarrheal with the largest turnover in 1984 was Imodium, which had over 10 percent of the market for antidiarrheals. Lomotil, Kaopectate, and Entero-Vioform made up another 10 percent (Health Action International 1986). A survey of dispensing patterns of seventy-five pharmacists in Bangladesh, Sri Lanka, and Yemen found that only 25 percent of pharmacies recommended ORS or referral to a health worker, but 65 percent dispensed drugs with or without ORS (Thomson and Sterkey 1986).

Treatment with ORT that is recorded cannot automatically be taken to mean ideal treatment. Rehydration solutions are normally prepared in the home—their effectiveness and safety

Table 5-11. Treatment Rates of Diarrhea Episodes in Children under Age Five in 276 Studies in 60 Countries
(percent)

Treatment	Treatment rates: Median	Range
ORS	26.4	0.0–53.0
Sugar-salt solutions	7.0	0.7–43.4
Home fluids	25.3	6.0–82.1
IV fluids	1.5	0.0–7.1
"Traditional" medicines	21.3	2.1–69.1
Other medicines	48.3	7.4–71.0
No treatment	15.3	5.0–64.1

Source: Unpublished World Health Organization data.

are highly dependent on how well informed and motivated mothers are, on their time availability, and on their access to the correct ingredients and utensils. Not all marketed oral rehydration fluids have the WHO-recommended composition and not all ORT is properly prepared or administered. Several studies have highlighted the difficulty of ensuring the correct preparation of SSS: 25 percent of samples prepared in Nepal (using the pinch-and-scoop method of measuring ingredients), 24 to 48 percent in Bangladesh, and 40 percent in Nigeria were found to be hypertonic, with sodium levels greater than 90, 100, and 80 millimolars, respectively (Poudayl and Thapa 1980; Chowdhury, Vaughan, and Abed 1988; and Nwoye, Uwagboe, and Madubuko 1988). There are also problems with incorrect use of solutions once they have been prepared, most commonly their underuse: in a study in Pakistan, 19 percent of mothers who used ORS stated that the dose should be one to two teaspoons given two to three times a day (Mull and Mull 1988). Similar findings were reported from Mozambique (Mozambique Ministry of Health and Eduardo Mondlane University Faculty of Medicine 1988).

These less-than-ideal practices (inadequate and incorrect use of ORT and use of other inappropriate treatments) contribute to the continuing high levels of death from diarrhea in children and give rise to unnecessarily high levels of side effects: 15 percent of diarrhea patients hospitalized in one children's hospital in Mexico City suffered from side effects associated with medication received prior to hospitalization (Phillips, Kumaté-Rodrígues, and Mota-Hernández 1989). They also contribute to a financial outlay that is higher than necessary: the annual global sale's value of "diarrhea drugs" is estimated at some $438 million (Health Action International 1986).

INSTITUTIONAL ASPECTS. Although, by and large, conclusions as to what constitutes appropriate case management are fairly straightforward, what governments and international organizations should be doing to ensure their adoption is less obvious. The fact that poor management of diarrhea cases continues in some areas points to the potential for improvement through the action of health and other ministries or international organizations. Governments have already made considerable progress. National diarrheal disease control programs, with the priority of implementing oral rehydration therapy as part of primary health services, are operational at various states of advancement in 100 countries, which include over 98 percent of the total population in the developing countries (WHO 1991).

Production and availability of ORS have increased rapidly during the past few years. The world supply of ORS reached the equivalent of about 350 million liters in 1989, over 70 percent of this quantity being locally produced in sixty-four developing countries (WHO 1991). The global rate of access to ORS has been estimated by WHO to have reached 63 percent in 1989. Training in diarrhea case management has also been supported. Data from developing countries indicate that 14 percent of community health workers have been trained in case management (WHO 1991). Most countries have legislation relating to the import, manufacture, and prescription of pharmaceuticals.

Although there is evidence that governments have made efforts to promote appropriate case management, there is clearly room for improvement. The World Health Organization (WHO 1991) has reported that the rate of use of ORS is still low in some countries (less than 20 percent in Sub-Saharan Africa), and there is evidence of inefficiency in the purchase, production, storage, and distribution of ORS. Soeters and Bannenberg (1988), for example, estimate that purchase through UNIPAC rather than currently used commercial sources would have allowed Gabon substantial savings in its drug bill. Even countries with pharmaceutical legislation rarely have the capacity to enforce it (WHO 1987d).

Unfortunately, it is not always clear what strategies are the most appropriate for governments to adopt. Although some studies have measured the costs and effectiveness of selected interventions, there is no comparable body of data that allows one, for example, to explore readily the relative merits of different methods of training staff, or of different pricing and legislative policies to control the production, importation, and marketing of, and the demand for, ineffective or dangerous drugs.

To date, international efforts have focused principally on attempts to promote ORT widely: ORT use rates have increased from below 1 percent in 1980 to 35 percent in 1989. This emphasis on a crucial life-saving intervention was an appropriate first priority and may have contributed to the decline in mortality. More attention needs to be paid to complementary efforts to discourage the use of costly, largely ineffective, and sometimes dangerous drugs. In addition, much greater efforts are needed to promote effective use of ORS, and effective ORT in general, with increased attention to feeding during diarrhea episodes and in the recovery period and the development of effective strategies of case management of dysenteric and persistent diarrheas. This constitutes the second most important priority for the WHO/CDD program (see also the subsection entitled "Institutional Aspects," under "Lowering Disease Incidence," above).

Defining an Optimal Strategy of Case Management

An optimal strategy of the case management of diarrhea in children should include correct fluid therapy, correct feeding therapy, appropriate use of antibiotics, no use of antidiarrheals, and effective education of the mother or caretaker. Correct fluid therapy should start at home. The mother or caretaker is the person available to initiate treatment when diarrhea begins. Home fluids, preferably containing sodium and a source of glucose and an osmolarity below 300 milliosmoles per liter, are recommended for the prevention of dehydration. If vomiting is present, more fluid should be offered, given in spoonfuls every three to five minutes. Dehydrated patients should be referred to a health facility and treated with ORS or, if severely dehydrated, with intravenous fluids. Feeding should be continued—breast milk for infants and nutrient-dense weaning foods for children who are already weaned. Food intake should be increased during the recovery period for nutritional rehabilitation. Antibiotics have a limited role in the treatment of diarrhea, being recommended only for the treatment of cholera and *Shigella* (visible blood in the stools is an adequate sign to indicate antimicrobial therapy against shigellosis, being more than 40 percent specific). Antidiarrheals should not be used in children. Effective case management also includes the education of the caretaker (a) to carry out fluid therapy; (b) to continue feeding during diarrhea and to increase feedings in the recovery period; (c) to avoid the use of antidiarrheal drugs; (d) to use antimicrobials correctly, if recommended; (e) to identify signs of severity of the disease, for rapid referral to health services; and (f) to prevent further diarrheal episodes, through breastfeeding, measles immunization, improved personal and domestic hygiene, and improved weaning practices.

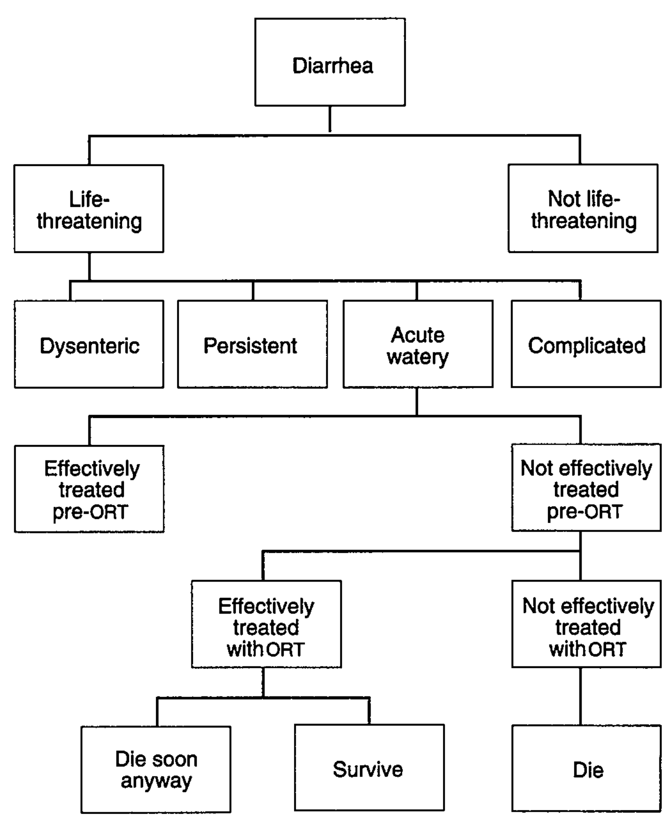
Strategies which governments could consider in attempts to encourage optimal treatment practices include education (for example, training pharmacists, changing medical curricula, initiating workshops for private medical practitioners), legislation to control the use of antidiarrheal drugs, and pricing policies that make prescribing of ORT financially attractive.

Priorities and Policies

Until now the emphasis of both international efforts and national programs in the field of diarrhea control has been almost exclusively on ORT. It has been widely claimed that, because dehydration is a primary cause of death in children with acute watery diarrhea, ORT programs can greatly reduce diarrhea mortality rates, and, because diarrhea accounts for 20 to 40 percent of all child deaths, ORT programs will also have a significant effect on overall child mortality rates.

With a decade of accumulated experience to draw upon, it is time to question these assumptions. At the heart of the issue is the estimate of the effect on child mortality from diarrhea or all causes that can be expected realistically from a good ORT program. Empirical evidence is very scarce and not easy to collect. Figure 5-2 presents a schematic view of the steps involved. Childhood diarrheas are first divided into those that are life-threatening and those that are not. The life-threatening diarrheas are made up of acute watery cases, persistent cases, dysenteric cases, and complicated cases (those with accompanying problems such as measles, malaria, or respiratory infection). The distribution of life-threatening cases among these four types is not documented. Oral rehydration therapy has its effect almost exclusively on the acute watery episodes. Figure 5-2 then distinguishes between those acute watery episodes that were effectively treated (for example, episodes in which the patient did not die) prior to ORT programs and those that were not. This is relevant to the effect on diarrhea and mortality from all causes that ORT programs will have. To have a greater effect on mortality, ORT must avert mortality not previously averted by other methods. Figure 5-2 then contrasts those effectively treated with those not effectively treated with ORT. As discussed previously, ineffective treatment may be rather common at present in many countries and may be amenable to substantial reduction. Finally, some of those effectively treated will die soon anyway from other causes (replacement or substitution mortality) and so will not contribute to reduction in mortality from all causes. The reader may substitute different speculative numbers in figure 5-2 to arrive at an estimate of the proportion of life-threatening diarrhea episodes averted or potentially averted by ORT. Even with the most optimistic assumptions, it is hard to produce a figure of more than 40 percent. The policy conclusions are clear: namely, much more emphasis should be

Figure 5-2. Role of ORT in Averting Mortality from Diarrhea



Source: Authors' design.

placed on primary prevention and on more comprehensive case management that would encompass all life-threatening episodes, including those that are persistent, dysenteric, and complicated.

In operational terms there are two important challenges for the 1990s. The first challenge is to put in place in all developing countries an effective system of case management for all diarrheas. This will involve going well beyond the focus on ORT to embrace nutritional management and correct use of drugs. Education of parents and training of health personnel will be key elements in any national program. For some dysenteric, persistent, and complicated diarrheas the results of research will be required before effective recommendations on case management can be made. The second challenge, and perhaps of as great priority, is the vigorous implementation of the available cost-effective preventive interventions. In particular these include measles vaccination, promotion of breastfeeding, improved hygiene and weaning practices, improved water and sanitation facilities, and the delivery of new vaccines as they become available.

For research, the priority is to support the operational priorities described above. Effective use of ORT, in both home and hospital settings, remains a poorly documented problem. The broader approach to case management requires a vigorous research agenda, ranging from the development of new drugs and studies on clinical efficacy to applied work on delivery and cost-effectiveness. For the preventive interventions we still need to know much more about design, delivery, sustainability, effectiveness, and costs. Research resources to date have focused largely on the development of technologies for diarrhea prevention and treatment. Additional attention needs to be given in the future to the means of application of these technologies. These research challenges can be met only from a strongly multidisciplinary perspective.

Notes

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1. All dollar amounts are 1982 U.S. dollars.

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